FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
Gastrointestinal Drugs Advisory Committee (GIDAC)
FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD
January 12, 2011

Draft Questions to Committee

The body of evidence submitted to establish the effectiveness of liprotamase for the proposed indication [treatment of patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF), chronic pancreatitis (CP), pancreatectomy, or other conditions] consists of clinical trials that primarily studied patients with cystic fibrosis. No children less than 7 years of age were entered in these clinical trials and the single randomized, placebo-controlled trial enrolled 64 pediatric patients ≥7 years (Study 726) and was only six weeks in duration. The long-term open label study (Study 767) did not have a prospectively defined control arm. The dose studied in the randomized, placebo-controlled trial was a fixed dose (not individually titrated).

Clinical outcome trials have not been required to support approval of porcine-derived pancreatic enzyme products (PEPs). Coefficient of fat absorption (CFA) has been accepted as a surrogate endpoint for PEPs based on the long history of use of these products and the existence of a body of literature that has linked the increase of fat absorption associated with PEPs with improvement in clinical outcome. However, the magnitude of change in CFA required to achieve improvement of clinical outcome has not been established. The magnitude of change in CFA associated with PEP products has ranged 26-41% in CF studies, and 47-61% in those studies in the subgroup of CF patients whose baseline CFA was <40%. If a threshold exists for CFA to serve as a surrogate, approval of a product associated with a treatment effect that does not reach that threshold could result in weight loss, impaired growth in children, and detrimental effects on lung function (in the setting of CF).

In light of the limitations of the studies and the absence of definitive information to establish the minimum magnitude of change in CFA that is necessary to achieve clinical benefit, we have the following questions to the Committee:

1. (a) **VOTE:** In the overall Study 726 population, is the observed difference in change in CFA between the liprotamase group (11%) and the placebo group (0.2%) of sufficient magnitude to be clinically meaningful? (please explain your vote)

   (b) **VOTE:** In the subgroup of patients with a baseline CFA <40% in Study 726, is the observed difference in change in CFA between the liprotamase group (20%) and the placebo group (5%) of sufficient magnitude to be clinically meaningful? (please explain your vote)

2. Do the results of Study 726 and the exploratory analyses of data from Study 767 (including comparisons to CFF Registry data) constitute substantial evidence of the efficacy of liprotamase for the treatment of patients with:
   (a) **VOTE:** EPI due to CF?
   (b) **VOTE:** EPI due to CF in children less than age 7 years?
   (c) **VOTE:** EPI due to CF in children ≥7 years of age?

Draft Questions to Committee (continued)

3. **VOTE:** For each of the approved porcine-derived PEPs, a short-term trial in patients with EPI due to CF supported an approved indication of EPI due to CF "…or other conditions" based on a large body of evidence in the literature. However, liprotamase is a new drug that differs from the porcine-derived PEPs and the majority of the patients studied in this application were CF patients, if you voted "yes" in response to Question 2 (a) above, do the data in this application support an indication for EPI due to conditions other than CF (e.g., chronic pancreatitis or pancreatectomy)?

4. **VOTE:** Are there additional efficacy studies that should be obtained prior to approving liprotamase for EPI? If yes, please describe the design of the studies (e.g., placebo-controlled, active-control, or dose-ranging), including selection of endpoints [e.g., change in CFA or clinical outcome such as growth parameters – height, weight, and body mass index (BMI)].

5. (a) **VOTE:** Are there safety concerns associated with the use of liprotamase in EPI (e.g., distal intestinal obstruction syndrome, fibrosing colonopathy, other) that preclude approval? If yes, please describe.

   (b) **VOTE:** Are there additional safety data or studies that should be obtained prior to approving liprotamase for EPI? If yes, please describe.

6. (a) **VOTE:** Based on currently available data, do the benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI? If yes, specify whether your answer is limited to particular subpopulation(s) defined by age or etiology of EPI.

   (b) **Discussion:** If you believe this product should be approved, are there any additional studies you would recommend post-approval?